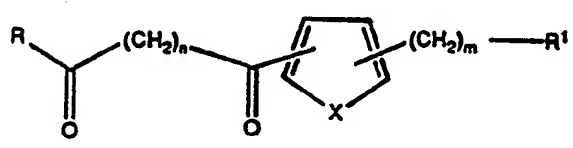




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(21) International Application Number: PCT/US92/03572 (22) International Filing Date: 6 May 1992 (06.05.92) (30) Priority data: 707,522 30 May 1991 (30.05.91) US (60) Parent Application or Grant (63) Related by Continuation US 707,522 (CIP) Filed on 30 May 1991 (30.05.91) (71) Applicant (for all designated States except US): G. D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : DJURIC, Stevan, Wakefield [GB/US]; 1023 Huber Lane, Glenview, IL 60025 (US). HAACK, Richard, Arthur [US/US]; 5356 North Luna, Chicago, IL 60630 (US). MIYASHIRO, Julie, Marion [US/US]; 1260 West Columbia, Chicago, IL 60626 (US).		(74) Agent: KOVACEVIC, Cindy, S.; G. D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i>
(54) Title: LTB4 SYNTHESIS INHIBITORS <div style="text-align: center;">  </div> (57) Abstract <p>This invention relates to a compound of formula (I), or a pharmaceutically acceptable salt thereof wherein X is oxygen, sulfur, -CH=CH-, or -CH=N-; wherein R¹ is -CO₂R² or tetrazole; wherein R² is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation; wherein R is an alkyl of from 1 to 20 carbons, -(CH₂)_pCF₃ or -(CH₂)_qR³ wherein R³ is alkoxy, phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons; wherein p and q are integers from 0 to 20; wherein n is 0 or 1; and wherein m is 0, 1, 2 or 3.</p>		

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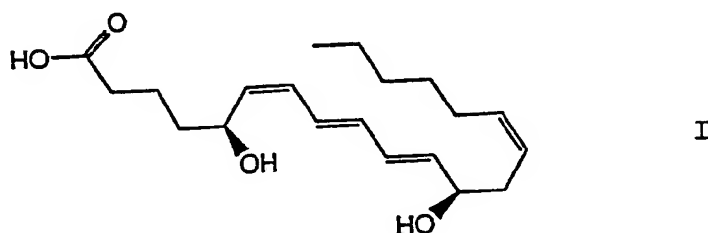
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Title: LTB₄ Synthesis InhibitorsBACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical agents (compounds) which act as leukotriene B₄ (LTB₄) synthesis inhibitors in mammals. The compounds inhibit LTB₄ synthesis by inhibiting phospholipase A₂ (PLA₂) activity. PLA₂ is an important enzyme in the biosynthesis of leukotrienes as PLA₂ acts to release arachidonic acid from phospholipids. Once released, arachidonic acid is rapidly metabolized by a variety of enzymes of the arachidonic acid cascade to produce prostaglandins, leukotrienes and related compounds. The use of the compounds herein to inhibit PLA₂ activity thus inhibits the release of arachidonic acid from phospholipids. The inhibition of release of arachidonic acid similarly diminishes subsequent products in the arachidonic acid cascade, such as prostaglandins, leukotrienes, and related compounds, including LTB₄.

LTB₄ (Formula I) is an arachidonic acid metabolite which is produced by the 5-lipoxygenase pathway. Pharmacologically, LTB₄ is an important mediator of



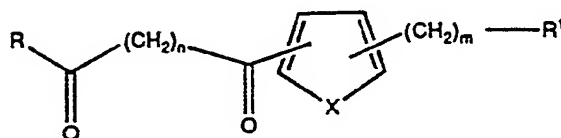
inflammation. LTB₄ is known to induce chemotaxis, chemokinesis, aggregation, and degranulation of leukocytes in vitro, and to induce accumulation of polymorphonuclear leukocytes, and increase vascular permeability and edema formation in vivo. Particularly high levels of LTB₄ are detected in lesions in inflammatory diseases such as rheumatoid or spondylarthritis, gout, psoriasis, ulcerative colitis, Crohn's disease, multiple sclerosis and some respiratory diseases. Since the compounds herein inhibit PLA₂ and thereby LTB₄ synthesis, the compounds of the present invention are useful in treating inflammatory conditions in mammals such as psoriasis, Crohn's disease, ulcerative colitis, multiple sclerosis and the like.

Accordingly, it is an object of this invention to produce compounds for use as pharmaceutical agents which will exhibit LTB₄ inhibitory activity in mammals.

The pharmacology of the biologically active leukotrienes is generally discussed in J. Clin. Invest. 73, 889-897 (1984).

SUMMARY OF THE INVENTION

This invention relates to a compound of the formula:



II

or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{N}-$;

wherein R^1 is $-\text{CO}_2\text{R}^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

$-(\text{CH}_2)_p\text{CF}_3$ or $-(\text{CH}_2)_q\text{R}^3$ wherein R^3 is alkoxy,

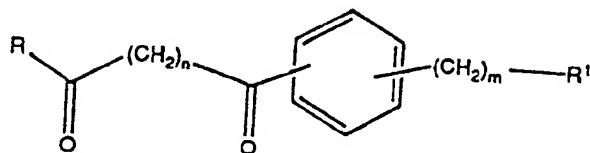
phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

This invention, more specifically, relates to a compound of the formula:



III

or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-CH=CH-$, or $-CH=N-$;

wherein R^1 is $-CO_2R^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

$-(CH_2)_pCF_3$ or $-(CH_2)_qR^3$ wherein R^3 is alkoxy,

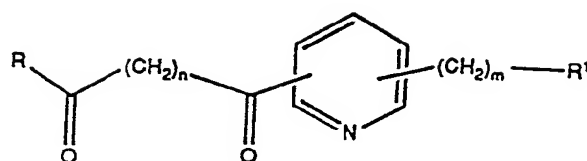
phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

This invention also relates to a compound of the formula:



IV

or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{N}-$;

wherein R^1 is $-\text{CO}_2R^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

$-(\text{CH}_2)_p\text{CF}_3$ or $-(\text{CH}_2)_qR^3$ wherein R^3 is alkoxy,

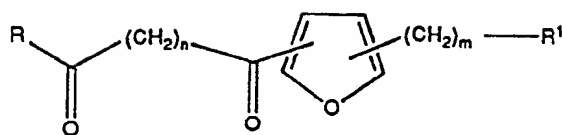
phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

This invention also relates to a compound of the formula:



V

or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{N}-$;

wherein R^1 is $-\text{CO}_2\text{R}^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

$-(\text{CH}_2)_p\text{CF}_3$ or $-(\text{CH}_2)_q\text{R}^3$ wherein R^3 is alkoxy, phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

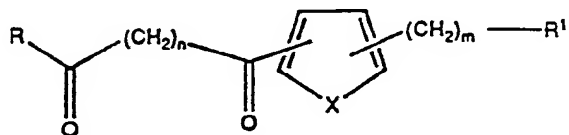
wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

DETAILED DESCRIPTION

This invention encompasses compounds of Formulae II-V as previously described. A particularly preferred embodiment of the present invention is encompassed by a compound of the formula:



VI

or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-CH=CH-$, or $-CH=N-$;

wherein R^1 is $-CO_2R^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

$-(CH_2)_pCF_3$ or $-(CH_2)_qR^3$ wherein R^3 is alkoxy, phenoxy or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

The term "lower alkyl" as used herein means straight or branched chain alkyls having 1-6 carbon atoms.

The term "pharmaceutically acceptable cation" as used to describe R^2 refers to cations such as ammonium, sodium, potassium, lithium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic, ammonium, tetraalkyl-ammonium, and the like.

The term "pharmaceutically acceptable salts" refers either to those non-toxic, base derived salts of any compound herein having a carboxylic acid function.

The base derived salts can be derived from pharmaceutically acceptable non-toxic inorganic or organic bases. Among the inorganic bases employed to produce pharmaceutically acceptable salts are the hydroxide bases of the "pharmaceutically acceptable cations" disclosed above.

Among the organic bases employed to produce pharmaceutically acceptable salts are the pharmaceutically acceptable non-toxic bases of primary, secondary, and tertiary amines. Especially preferred non-toxic bases are isopropylamine, diethylamine, ethanolamine, dicyclohexylamine, choline, and caffeine.

All of the pharmaceutically acceptable salts are prepared by conventional processes which are well known to those of ordinary skill in the art.

The compounds of this invention are generally prepared according to the reaction schemes I, II and III, wherein a side chain is substituted onto a halo aromatic acid or ester moiety. By halo is meant a halogen such as bromo, iodo or chloro. In Scheme I, the halo group is represented by the term "halo." By aromatic moiety is meant phenyl, pyridyl, thienyl or furyl, corresponding to "X" in the aryl ring being $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-$, $-\text{S}-$, and $-\text{O}-$.

As disclosed in the following reaction Schemes I-IV, an alkyne side chain can be added to an aromatic moiety by different techniques. The alkyne side chain is then hydrated with sulfuric acid, water and mercuric oxide to yield the indicated diketo product.

In Scheme I the alkyne side chain is added by performing a nucleophilic substitution of the halogen such as via a coupling reaction with an alkyne, CO, and $\text{Pd}[\text{O}]$. In Scheme II the alkyne side chain is added by acylation of a trimethylsilyl (TMS) acetylide with a diacid chloride in the presence of AlCl_3 . In Scheme III the alkyne side chain is added via nucleophilic attack of an acetylide anion on an aldehyde with subsequent oxidation of the resulting alcohol.

In Scheme IV the alkyne side chain is added via nucleophilic attack of an acetylide anion on an acid chloride.

The biological activity possessed by the compounds of this invention was indicated by positive results in assays for inhibition of human synovial fluid PLA₂ (HSF-PLA₂) and LTB₄ biosynthesis in HL-60 cells.

By virtue of their activity as LTB₄ synthesis inhibitors, the compounds of Formula I-VI are useful in treating inflammatory conditions in mammals such as psoriasis, Crohn's disease, ulcerative colitis, multiple sclerosis and the like. Similarly, the compounds of Formula I-VI can be used in preventing recurring inflammatory attacks. A physician or veterinarian of ordinary skill can readily determine whether a subject exhibits the inflammatory condition. The preferred utility relates to treatment of ulcerative colitis.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules, soft gels, pills, powders, granules, elixirs, or syrups.

The compounds can also be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly, or topically using forms known to the pharmaceutical art. Moreover, they can be administered rectally or vaginally, in such forms as suppositories or bougies. In general, the preferred form of administration

is oral. For the orally administered pharmaceutical compositions and methods of the present invention, the foregoing active ingredients will typically be administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, soft gels, elixirs, syrups, drops, and the like, and consistent with conventional pharmaceutical practices.

For example, for oral administration in the form of tablets or capsules, a therapeutically effective amount of one or more compounds of the present invention can be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, and the like, or various combinations thereof. For oral administration in liquid forms, such as in soft gels, elixirs, syrups, drops and the like, a therapeutically effective amount of the active drug components can be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as water, saline, ethanol, polyethylene glycol, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, various buffers, and the like, or various combinations thereof. Moreover, when desired or necessary, suitable binders, lubricants,

disintegrating agents, and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol, and waxes, or combinations thereof. Lubricants for use in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like, or combinations thereof. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, and the like, or combinations thereof. Sweetening and flavoring agents and preservatives can also be included where appropriate.

For intravascular, intraperitoneal, subcutaneous, or intramuscular administration, one or more compounds of the present invention can be combined with a suitable carrier such as water, saline, aqueous dextrose, and the like. For topical administration, such as for psoriasis, therapeutically effective amounts of one or more compounds of the present invention can be combined with pharmaceutically acceptable creams, oils, waxes, gels and the like. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those skilled in the art. The compounds can also be formulated using pharmacologically

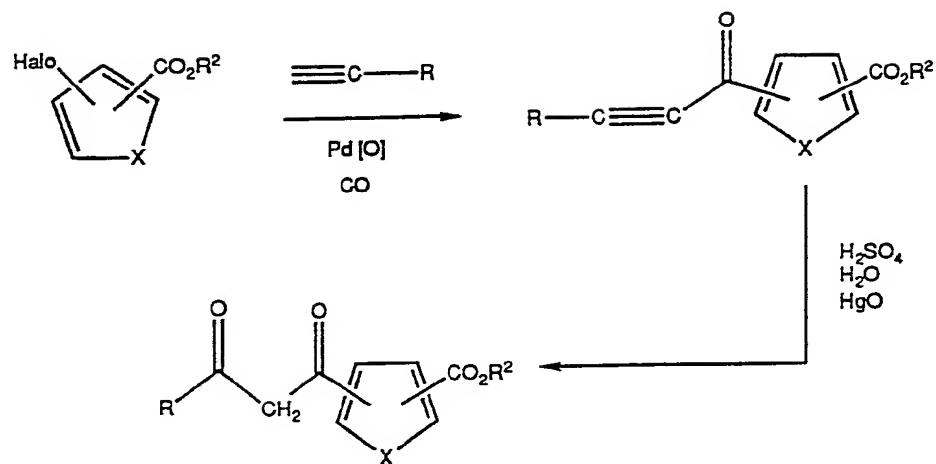
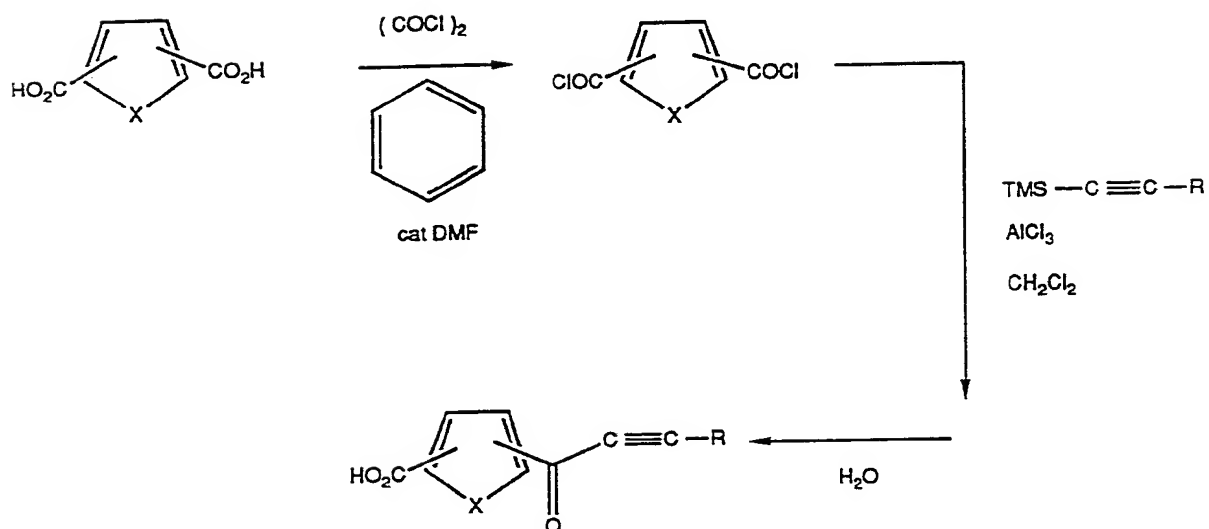
acceptable base addition salts. Moreover, the compounds or their salts may be used in a suitable hydrated form.

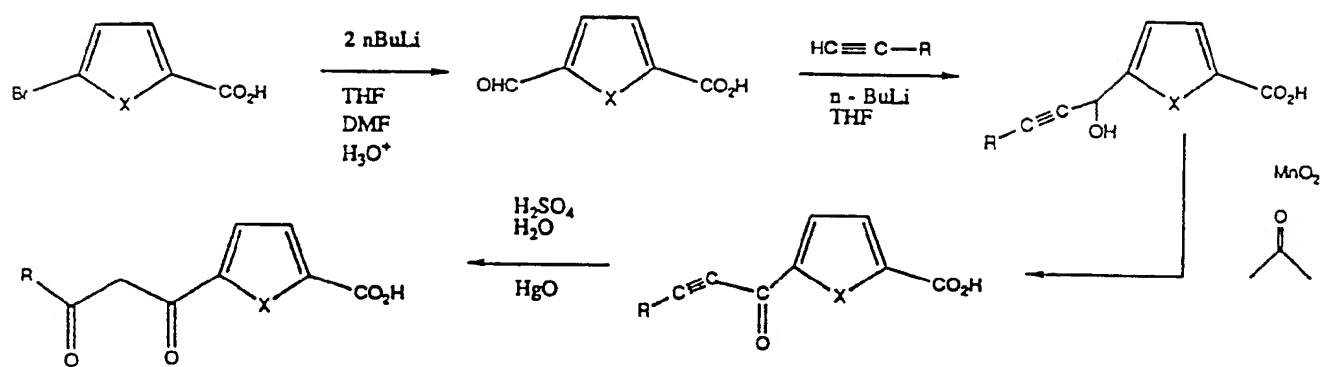
Regardless of the route of administration selected, a non-toxic but therapeutically effective quantity of one or more compounds of this invention is employed in any treatment. The dosage regimen for preventing or treating inflammatory conditions with the compounds of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, and medical condition of the patient, the severity of the inflammatory condition, the route of administration, and the particular compound employed in the treatment. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent or arrest the progress of the condition. In so proceeding, the physician or veterinarian could employ relatively low doses at first and sequentially increase the dose until a maximum response is obtained. Daily dosages of the compounds of the invention are ordinarily in the range of about 1.0mg/kg up to about 30.0 mg/kg, (preferably in the range of about 2.0 to 14.0 mg/kg (orally)).

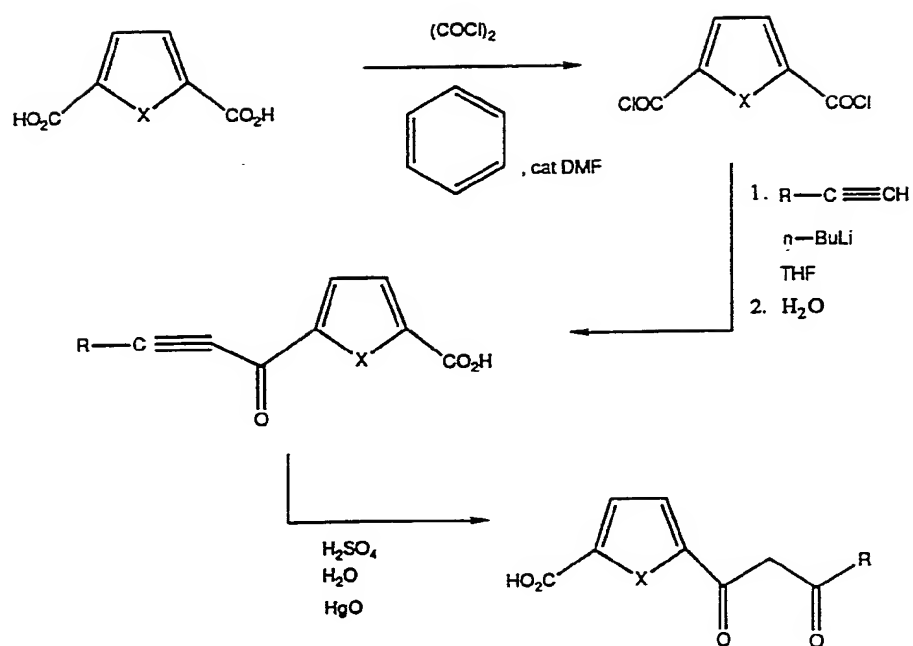
The following examples illustrate the methods used to prepare the compounds of this invention. These examples are given by way of illustration only and are not meant to be construed as limiting the invention in spirit or in scope,

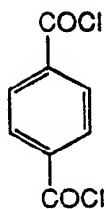
as many modifications in materials and methods will be apparent from this disclosure to those skilled in the art.

In the structures herein a bond drawn across a bond in a ring indicates that the bond can be to any available carbon atom of the ring structure.

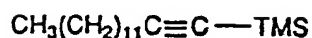
Scheme IScheme II

Scheme III

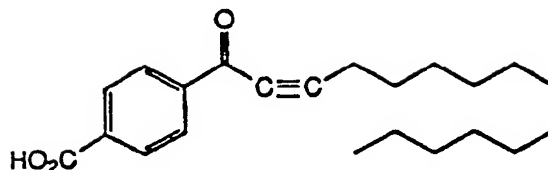
Scheme IV

Example 1

The above acid chloride was prepared from terephthalic acid by reacting 0.5g (3 mmoles) of terephthalic acid with 2cc of $[\text{COCl}]_2$ (23.6 mmoles) in 10cc of benzene and with one drop of dimethylformamide. The reagents were mixed and warmed to 60°C for twenty-four hours. The reaction mixture was cooled to room temperature and the volatile components were removed in vacuo to give the above compound as a pale yellow solid.

Example 2

The above compound was prepared by reacting an acetylene of the formula $\text{CH}_3(\text{CH}_2)_{11}\text{C}\equiv\text{CH}$ (2.5g, 12.87 mmoles) which was added to 25cc of tetrahydrofuran (THF) and 50mg of triphenylmethane (Ph_3CH) which was added as an indicator. The solution was cooled to -30°C and 1.6 molar n-butyllithium (n-BuLi) was added dropwise until the solution turned red. Approximately 8.5cc of n-BuLi was added. The solution was back titrated with the acetylene compound until it became colorless. The solution was cooled to -78°C and 2cc (15.75 mmoles) of trimethylsilyl chloride (TMS-Cl) was added. The solution was slowly warmed over a period of five hours to room temperature. The reaction was quenched with water and extracted with hexane. The hexane was washed once with water and once with brine and dried over magnesium sulfate (MgSO_4). The trimethylsilyl compound was isolated in an amount of 4.31g (16.2 mmoles).

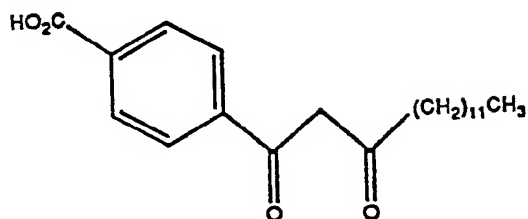
Example 3

The above compound was prepared by reacting 3 mmoles of the acid chloride product from Example 1 with 0.8g (3 mmoles) of the TMS-acetylene product from Example 2. The acid chloride and the TMS-acetylene product were dissolved in 10cc of dichloromethane and cooled to 0°C. To the reaction mixture was added 0.8g (6 mmoles) of aluminum chloride (AlCl₃) in small portions over ten minutes. The reaction mixture was stirred for about 1.5 hours at 0°C. The reaction was quenched with ice and the mixture was extracted three times with diethyl ether. The extracts were combined and washed once with water and once with brine (saturated NaCl solution) and dried over magnesium sulfate. Removal of the solvent in vacuo yielded 0.29g of the above product. This was chromatographed on silica eluting with 15% ethyl acetate - 85% hexane.

HRMS (M⁺): calculated 342.2195; found 342.2196

Example 4

4-(1,3-dioxohexadecanyl)benzoic acid



The product of Example 3, 27mg was treated with 2ml of cold H_2SO_4 which had been cooled in an ice bath. The mixture was stirred until all of the product had dissolved. To the reaction mixture was added 1mg HgO . The reaction mixture was maintained cool in an ice bath. Two drops of water were added to the reaction mixture. The ice bath was removed and the reaction mixture was stirred and allowed to warm to room temperature for one half hour. The mixture was cooled to 0°C and quenched with ice. The reaction mixture was diluted with water and extracted twice with ethyl acetate. The collected extracts were washed twice with water. The washed ethyl acetate fractions were collected and the volatile components removed and the residue chromatographed on silica gel (gradient elution) with 5% isopropyl alcohol, 95% Hexane +1%

HOAc then 10% isopropyl alcohol, 90% Hexane +1% HOAc
as eluant. 0.017g of the above product was isolated.

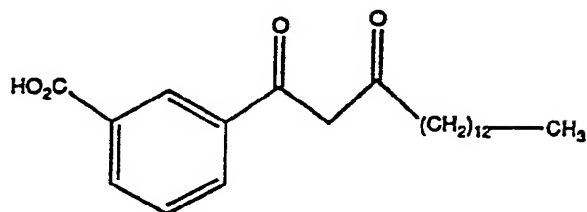
Analysis:

Calculated for $5H_2O$: C, 71.51; H, 9.00

Found: C, 71.80; H, 8.72

Example 5

3-(1,3-dioxohexadecanyl)benzoic acid



The above compound was prepared by mixing 9.42g of m-iodobenzoic acid (38 mmoles) and 8g (38.4 mmoles) of an acetylene derivative of the formula

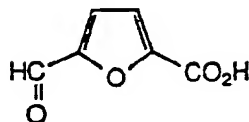


with 0.27g (0.38 mmoles) of a palladium catalyst, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in 100cc of diisopropyl amine. The reaction vessel was purged with carbon monoxide. The reaction mixture was heated under a carbon monoxide atmosphere (atmospheric pressure, balloon) in an oil bath at 80°C for two hours. The reaction mixture was cooled to room temperature. The volatile components were removed in vacuo and the residue was taken up in 5% hydrochloric acid and extracted with diethyl ether.

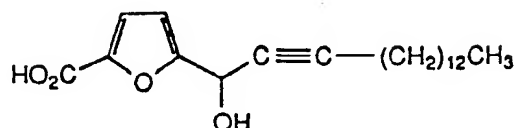
The diethyl ether was washed once with 10% hydrochloric acid, twice with water, and once with a brine solution and dried over magnesium sulfate. The solvent was removed yielding 18.65gm of the product. A solid component was isolated from this mixture by chromatography on silica gel (10% isopropyl alcohol, 90% hexane, 1% HOAc). Recrystallization from CH_2Cl_2 /Hexane afforded 0.66g of the above product.

Analysis calculated: C, 73.76; H, 9.15

Found: C, 73.40; H, 9.13

Example 6

The above compound was prepared by forming a solution of 2.5 g (13.1 mmoles) of a bromo-furanoic acid in 25ml of tetrahydrofuran (THF) which was cooled to -78°C . To the solution was added a 1.6 molar solution of n-butyl lithium in hexane (17.5ml, 28 mmoles) which was stirred at -78° for one hour. Dimethylformamide (DMF) was added in an amount of 2.4 ml (30 mmoles). The solution was allowed to warm to room temperature. The reaction mixture was quenched with water and acidified with 10% hydrochloric acid. The resultant reaction mixture was extracted twice with ethyl acetate, the combined extracts were washed twice with water and once with brine and subsequently dried over magnesium sulfate. An orange solid was obtained after removal of the solvent in vacuo. Following chromatography on silica gel (gradient elution with EA-Hexane containing 1% HOAc) 0.73 gms. of the compound of the above formula was obtained.

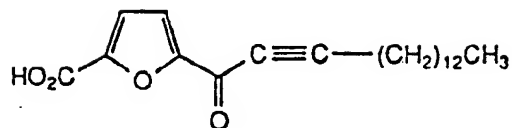
Example 7

The above compound was prepared by forming a solution of 1.25g (6 mmoles) of an acetylene of the formula $\text{H}\equiv(\text{CH}_2)_{12}\text{CH}_3$ in 25 ml. THF which contained 20 mg. of triphenylmethane which was added as an indicator. The solution was cooled to -50°C and then treated with 3.75 ml. (6 mmoles) of $n\text{-BuLi}$ until the red color of the triphenylmethane anion persisted. A few drops of the acetylene compound was added until the color disappeared. An amount of 0.42 gms. of the product formed in Example 6 in 10 ml. THF was added drop-wise to the solution. The mixture was warmed to 0°C over one-half hour. The mixture was quenched with water and acidified with 10% hydrochloric acid. The aqueous phase was extracted twice with ethyl acetate. The extracts were combined and washed twice with water and once with brine and were dried over magnesium sulfate. Chromatography on silica gel (gradient elution with

EA-Hexane containing 1% HOAc) yielded 0.80 gms. of a pale yellow solid.

HRMS (M^+) Calculated: 348.2301;

Found: 348.2291.

Example 8

The compound was prepared by reacting 0.145 g. (4.2 mmoles) of the product from Example 7 in acetone (25 ml) and adding 1.5 g. of activated MnO_2 portionwise over five minutes. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was poured into 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed once with water and dried over magnesium sulfate. After the solvent was removed in vacuo a white solid remained. Following chromatography on silica gel (gradient elution with EA-Hexane containing 1% HOAc), 60 mg. of a white solid was recovered.

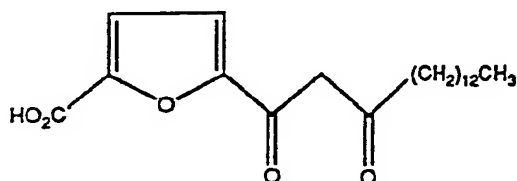
Analysis (for hydrate with 0.35 H_2O)

Calculated: C, 71.50; H, 8.77

Found: C, 71.55; H, 8.63

Example 9

5-(1,3-dioxohexadecanyl)-2-furancarboxylic acid



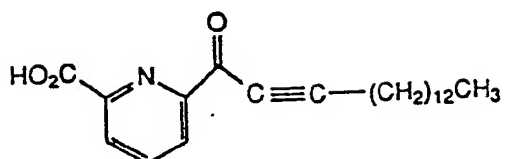
The product of Example 8, 22.5mg was treated with 1ml of cold H_2SO_4 which had been cooled in an ice bath. The mixture was stirred until all of the product had dissolved. To the reaction mixture was added 1mg HgO . The reaction mixture was maintained cool in an ice bath. Two drops of water was added to the reaction mixture. The ice bath was removed and the reaction mixture was stirred and allowed to warm to room temperature for one half hour. The mixture was cooled to 0° and quenched with ice. The reaction mixture was diluted with water and extracted twice with ethyl acetate. The collected extracts were washed twice with water. The washed ethyl acetate fractions were collected and the volatile components removed and the residue chromatographed on silica gel (gradient elution) with 5% isopropyl alcohol, 95% Hexane +1%

HOAc then 10% isopropyl alcohol, 90% Hexane +1% HOAc,
which yielded 0.018g of the above product.

Analysis: For 0.75 H₂O

Calculated: C, 66.73; H, 8.93

Found: C, 66.69; H, 8.74

Example 10

The above compound was prepared by forming a solution of 0.83 gms. (4 mmoles) of an acetylene of the formula $\text{H}-\text{C}\equiv\text{C}-(\text{CH}_2)_{12}\text{CH}_3$ in 25 ml. THF containing 20 mgs. of triphenyl methane as an indicator. The solution was cooled to -50°C , then treated with 2.5 ml. of a 1.6 molar solution (4 mmoles) of $n\text{-BuLi}$ in hexane until the red color of the triphenylmethane anion persisted. A few drops of the acetylene was added until the color disappeared. The resultant lithium acetylide preparation was cooled to -78°C . A solution (6 mmoles) of a diacid chloride of the formula

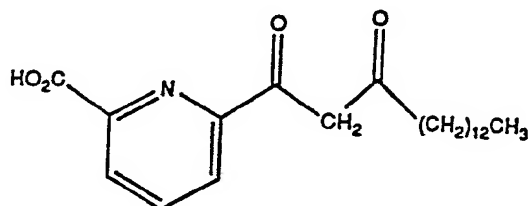
prepared from the corresponding diacid and oxalyl chloride in benzene (catalytic DMF) was cooled to -78°C and the -78°C solution of lithium acetylide was added dropwise via a cannula. The reaction was stirred for 10 minutes and quenched with water and warmed to room temperature. The reaction mixture was poured into water and acidified with acetic acid (HOAc). The aqueous solution was extracted twice with ethyl acetate and the extracts were washed twice with water, once with brine and dried over magnesium sulfate. Following chromatography on silica gel (gradient elution with isopropyl alcohol- hexane), 0.95 gms. of a product of the above formula was recovered.

Analysis calculated: C, 73.92; H, 8.74; N, 3.92

Found: C, 73.64; H, 8.79; N, 3.86

Example 11

6-(1,3-dioxohexadecanyl)-2-pyridinecarboxylic acid



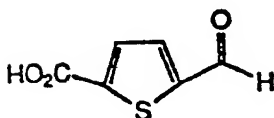
The product of Example 10, 25.6mg was treated with 2ml of cold H_2SO_4 which had been cooled in an ice bath. The mixture was stirred until all of the product had dissolved. To the reaction mixture was added 1mg HgO . The reaction mixture was maintained cool in an ice bath. Two drops of water was added to the reaction mixture. The ice bath was removed and the reaction mixture was stirred and allowed to warm to room temperature for one half hour. The mixture was cooled to 0° and quenched with ice. The reaction mixture was diluted with water and extracted twice with ethyl acetate. The collected extracts were washed twice with water. The washed ethyl acetate fractions were collected and the volatile components removed and the residue chromatographed on silica gel (gradient elution) with 5% isopropyl alcohol, 95% Hexane +1%

HOAc then 10% isopropyl alcohol, 90% Hexane +1% HOAc,
which yielded 0.026g of the above product.

Analysis: For $0.8H_2O$

Calculated: C, 67.77; H, 8.94; N, 3.59.

Found: C, 67.71; H, 8.53; N, 3.43.

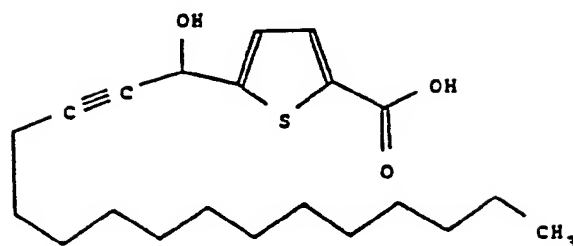
Example 12

A compound of the above formula was prepared in the following manner. To a cooled (0°C) solution of 5.5 ml. (39.2 mmoles) of diisopropylamine in 50 ml. of THF was added 20.5 ml. of 1.6 molar BuLi (32.8 mmoles) to make 32.8 mmoles of lithium diisopropylamide (LDA). The reaction mixture was stirred for one-half hour at 0°C and cooled to -78°C. To the mixture was added 2.1g (16.4 mmoles) of 2-thiophene carboxylic acid in 25 ml. THF. Additional THF was added to increase the volume to 200 ml. and the reaction mixture was stirred for one-half hour. DMF was added in an amount of 1.3 ml. (16.8 mmoles). The reaction mixture was warmed to room temperature and stirred for 1 1/2 hours. The reaction mixture was quenched with water and acidified with 1N hydrochloric acid and extracted with ethyl acetate. The organic extracts were

combined and dried over magnesium sulfate. The resultant mixture was filtered and stripped to yield a yellow solid. Separation using chromatography on silica eluting with ethyl acetate/hexane/1% acetic acid provided 1.3 gms. of a yellow solid of the above formula. MP 160-163°.

Analysis calculated: C, 46.15; H, 2.58

Found: C, 46.11; H, 2.82

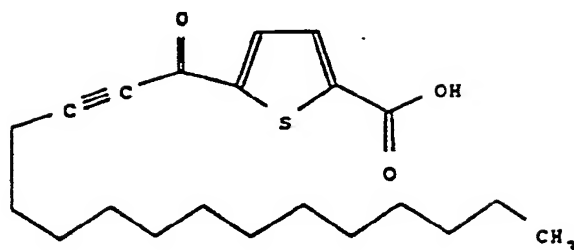
Example 13

The compound with the above structure was prepared in the following manner. An acetylene of the formula $\text{H}-\text{C}\equiv\text{C}-(\text{CH}_2)_{12}\text{CH}_3$ in an amount of 549.3 mg. (2.6 mmoles) in 15 ml. of THF was cooled to -20° . To the solution was added 1.6 ml. (2.6 mmoles) of n-BuLi. The reaction was stirred for one half hour and 203.4 mg. (1.3 mmoles) of the product from Example 13 in 10 ml. of THF was added. The mixture was stirred and maintained at -20° for 15 minutes and allowed to warm to 0°C and stirred for one-half hour. The reaction mixture was quenched with water and acidified with 10% hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate. The extract was filtered and stripped to yield a yellow oil which solidified upon standing. The solid was dissolved in ethyl acetate and filtered through silica gel eluting with 100%

hexane followed by ethyl acetate in 1% acetic acid. The ethyl acetate fraction yielded 392.8 mg. of the above compound as a yellow solid having a melting point of 75-90°.

Analysis calculated: C, 69.19; H, 8.85

Found: C, 69.18; H, 9.02

Example 14

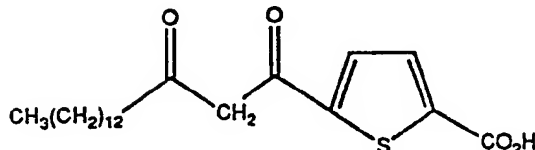
A compound of the above structure was formed in the following manner. 7.2 mg. (0.020 mmoles) of the compound prepared in Example 13 was dissolved in 1 ml. acetone. To the solution was added 72 mg. (0.83 mmoles) of activated manganese dioxide. The reaction mixture was stirred vigorously at room temperature overnight. The reaction mixture was poured into 10% hydrochloric acid. The aqueous phase was extracted with ethyl acetate. The organic washes were combined and dried over magnesium sulfate. The organic phase was filtered and stripped to yield 6 mg. (0.010 mmoles) of the above product as a white solid.

HRMS (M^+) Calculated: 362.1916

Found: 362.1910

Example 15

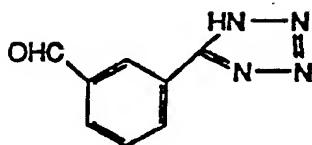
5-(1,3-dioxohexadecyl)-2-thiophenecarboxylic acid



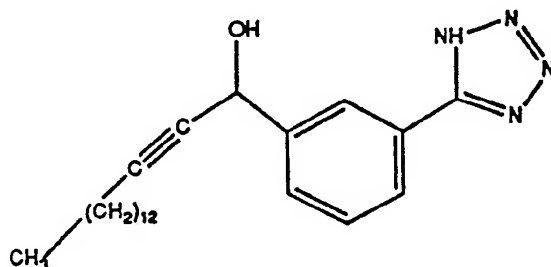
The compound of Example 14 (29.0 mg, 0.080 mmol) was dissolved in 2 ml of cold sulfuric acid. The reaction mixture was stirred until all of the solid dissolved. Two drops of water were added. After stirring for 10 minutes, the reaction mixture was placed in an oil bath at 60° C for 1 hour. The mixture was cooled to 0° C and quenched with ice. The aqueous phase was extracted three times with 20 ml ethyl acetate. The combined organic extracts were washed with saturated NaHCO₃ and dried over MgSO₄. The resultant oil was filtered through silica gel eluting with EA/1% acetic acid to yield 14.2 mg (0.037 mmol) of the above compound as a yellow solid.

HRMS (M⁺) Calculated: 380.2022

Found: 380.1993

Example 16

A compound having the above formula was prepared in the following manner. Two grams (15.2 mmoles) of m-cyano-benzaldehyde along with 2.98 gms. (45.8 mmoles) of NaN_3 and 2.9 gms. (21.1 mmoles) of $\text{Et}_3\text{N} \cdot \text{HCl}$, were dissolved in 50 ml. of 1-methyl-2-pyrrolidinone. The reaction mixture was refluxed under argon. After 1 hour and 45 minutes the reaction mixture was cooled to room temperature and poured into 200 ml. of water and acidified with 10% hydrochloric acid. The reaction mixture was extracted with successive ethyl acetate washes. The ethyl acetate extracts were combined and washed with brine and dried over magnesium sulfate. The ethyl acetate extract was chromatographed through silica gel, yielding 0.3 gms. of the product having the above formula as a white solid.

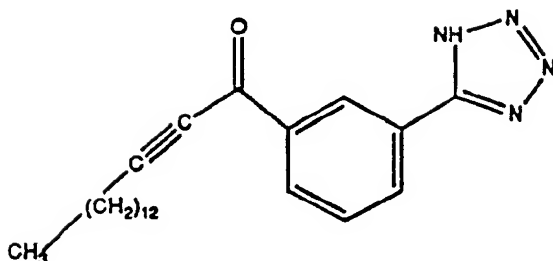
Example 17

A compound of the above formula was prepared in the following manner. A solution of 542mg (2.6 mmoles) of an acetylene of the formula $\text{HC}\equiv\text{C}(\text{CH}_2)_{12}\text{CH}_3$ was dissolved in 100ml THF and cooled to -30°C . To the solution was added 1.6 ml. (2.6 mmoles) of a 1.6 molar n-BuLi solution which was added dropwise. The reaction mixture was stirred for 15 minutes at which time 219mg. (1.26 mmoles) of the product from Example 16 dissolved in 8 ml. of THF was added dropwise. The solution was stirred and maintained at -30°C for one-half hour, then warmed to room temperature. The reaction mixture was quenched with water and acidified with 10% hydrochloric acid. The layers were separated and the organic phase was washed with brine and dried over sodium sulfate. The layer was filtered and stripped to yield a yellow solid which upon

chromatography over silica gel yielded 171.2mg. of the above product as a white solid. M.P. 108-110°C.

Analysis calculated: C, 72.21; H, 8.96; N, 14.65

Found: C, 72.03; H, 9.00; N, 14.77

Example 18

The compound having the above formula was prepared in the following manner. A solution was prepared by dissolving 36.2 mg (0.095 mmoles) of the product from Example 17 in acetone. To the solution was added 360 mg (4.14 mmoles) of activated manganese dioxide. The reaction mixture was stirred vigorously at room temperature overnight. The reaction mixture was poured into 10% hydrochloric acid. The aqueous phase was extracted with ethyl acetate and the organic washes were combined and dried over magnesium sulfate. The organic phase was filtered and stripped to yield 18 mg. of a pale yellow solid of a compound having the above formula.

Analysis calculated: C, 72.59; H, 8.48; N, 14.72

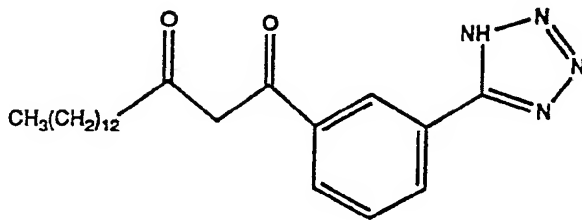
Found: C, 72.19; H, 8.66; N, 14.13

HRMS (M⁺) Calculated: 380.2576

Found: 380.2579

Example 19

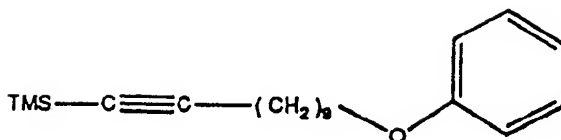
1-[3-(1H-tetrazol-5-yl)phenyl]-1,3-hexadecadione



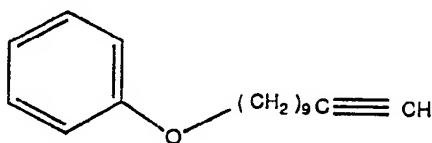
To 8mg (0.021 mmol) of the compound produced in Example 18 was added 10 drops of cold H₂SO₄. The reaction mixture was stirred for 5 minutes at which time about 1mg of HgO was added. The reaction mixture was stirred at room temperature for 45 min. Water and ethyl acetate were added. The organic phase was washed with saturated NaHCO₃. The organic phase was collected and dried over MgSO₄. The organic phase was filtered and vacuum stripped to yield 7.6mg of white solid.

HRMS (M⁺) Calculated: 398.2682

Found: 398.2683

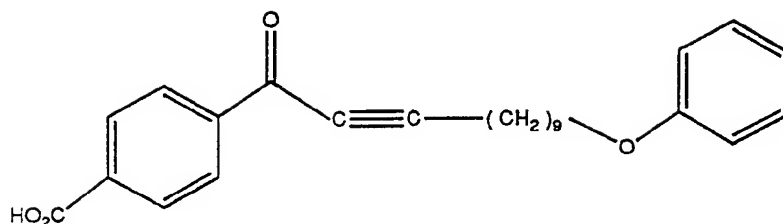
Example 20

The above compound was prepared by reacting 2g of phenol (21.2 mmol), 3.58g of 10-undecyn-1-ol (21.2 mmol) and 5.57g of triphenylphosphine (21.2 mmol) with stirring in 40 mls of tetrahydrofuran (THF) at room temperature under argon. A solution of 3.7g diethyl azodicarboxylate (21.2 mmol) was added dropwise to the reaction mixture at room temperature. The solution was allowed to stand overnight. The reaction mixture was concentrated, dissolved in ether, filtered and concentrated. This yielded 3.5g of the acetylene product having the following formula



A 1g portion of the above acetylene product (4.09 mmol) was dissolved in 25 ml of THF and 10 mg of triphenyl methane was added as an indicator. The solution was cooled to -30° C and 2.6 ml of 1.6M n-butyl lithium (4.1 mmol) was added dropwise until the solution turned red. The solution was back-

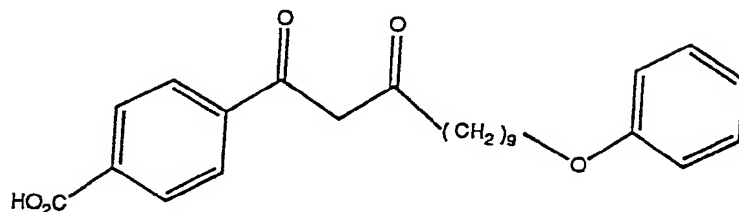
titrated with the acetylene product until colorless. The solution was cooled to -78°C and 2ml of trimethylsilyl chloride (15.8 mmol) was added. The solution was slowly warmed to room temperature. The reaction was quenched with water and extracted with hexane. The hexane extract was washed once with water and once with brine and dried over MgSO_4 . The above product was recovered in an amount of 1.26g.

Example 21

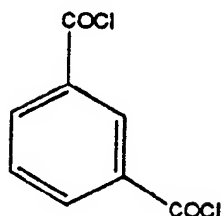
The above compound is prepared by reacting 3 mmoles of the acid chloride product from Example 1 with 0.95g (3 mmoles) of the TMS-acetylene product from Example 20. The acid chloride and the TMS-acetylene product are dissolved in 10cc of dichloromethane and cooled to 0°C . To the reaction mixture is added 0.8g (6 mmoles) of aluminum chloride (AlCl_3) in small portions over ten minutes. The reaction mixture is stirred for about 1.5 hours at 0°C . The reaction is quenched with ice and the mixture is extracted three times with diethyl ether. The extracts are combined and washed once with water and once with brine (saturated NaCl) and dried over magnesium sulfate. Removal of the solvent in vacuo yields the above product.

Example 22

4-(1,3-dioxo-12-phenoxydodecyl)benzoic acid



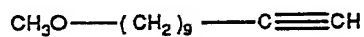
The product of Example 21, 27mg is treated with 2ml of cold H_2SO_4 which has been cooled in an ice bath. The mixture is stirred until all of the product has dissolved. To the reaction mixture is added 1mg HgO . The reaction mixture is maintained cool in an ice bath. Two drops of water are added to the reaction mixture. The ice bath is removed and the reaction mixture is stirred and allowed to warm to room temperature for one half hour. The mixture is cooled to 0°C and quenched with ice. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The collected extracts are washed twice with water. The washed ethyl acetate fractions are collected and the volatile components removed and the residue chromatographed on silica which yields the above product.

Example 23

The above acid chloride was prepared from isophthalic acid by reacting 0.5g (3 mmoles) of isophthalic acid with 2cc of $[\text{COCl}]_2$ (23.6 mmoles) in 10cc of benzene and with one drop of dimethylformamide. The reagents were mixed and warmed to 60°C for twenty-four hours. The reaction mixture was cooled to room temperature and the volatile components were removed in vacuo to give the above compound.

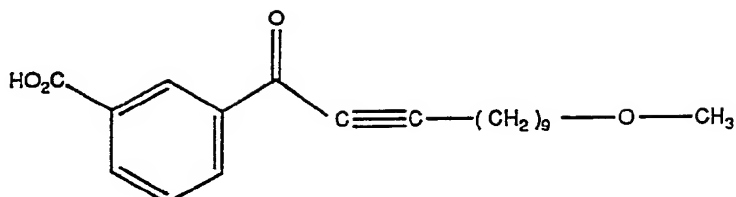
Example 24

The above product was prepared by placing 1g of hydroxy acetylene (5.94 mmol) in 10 ml of THF and cooling to 0°C. To the solution was added 1 ml of methyl iodide which was followed by the portionwise addition of 0.4g of sodium hydride (8.33 mmol). The reaction mixture was stirred and warmed to room temperature overnight. The reaction was quenched by pouring in to 100ml of water, then extracted with hexane. The hexane was washed once with water and once with brine and dried over magnesium sulfate. Removal of the solvent in vacuo yielded 1.21g of a pale yellow oil acetylene product of the following formula



A 1g portion of the above acetylene product (5.5 mmol) was dissolved in 25 ml of THF and 10 mg of triphenyl

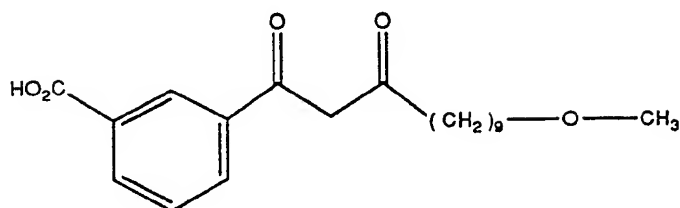
methane was added as an indicator. The solution was cooled to -30°C and 3.4 ml of 1.6M n-butyl lithium (4.1 mmol) was added dropwise until the solution turned red. The solution was back-titrated with the acetylene product until colorless. The solution was cooled to -78°C and 2ml of trimethylsilyl chloride (15.8 mmol) was added. The solution was slowly warmed to room temperature. The reaction was quenched with water and extracted with hexane. The hexane extract was washed once with water and once with brine and dried over MgSO_4 . The above product was recovered in an amount of 1.26g.

Example 25

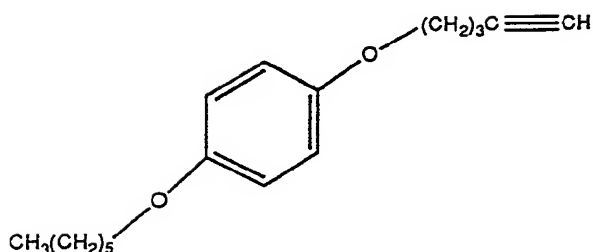
The above compound is prepared by reacting 3 mmoles of the acid chloride product from Example 23 with 0.76g (3 mmoles) of the TMS-acetylene product from Example 24. The acid chloride and the TMS-acetylene product are dissolved in 10cc of dichloromethane and cooled to 0°C. To the reaction mixture is added 0.8g (6 mmoles) of aluminum chloride (AlCl₃) in small portions over ten minutes. The reaction mixture is stirred for about 1.5 hours at 0°C. The reaction is quenched with ice and the mixture is extracted three times with diethyl ether. The extracts are combined and washed once with water and once with brine (saturated sodium bicarbonate solution) and dried over magnesium sulfate. Removal of the solvent in vacuo yields 0.29g of the above product.

Example 26

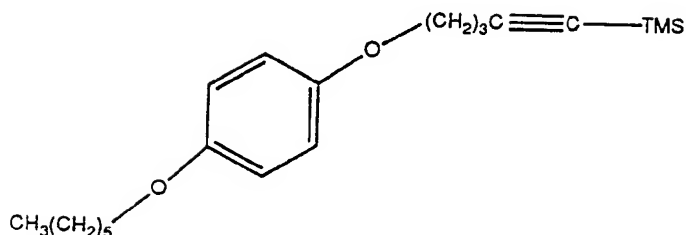
3-(12-methoxy-1,3-dioxododecyl)benzoic acid



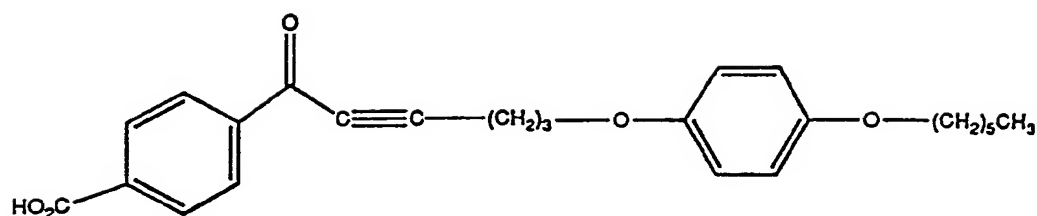
The product of Example 25, 27mg is treated with 2ml of cold H_2SO_4 which has been cooled in an ice bath. The mixture is stirred until all of the product has dissolved. To the reaction mixture is added 1mg HgO . The reaction mixture is maintained cool in an ice bath. Two drops of water are added to the reaction mixture. The ice bath is removed and the reaction mixture is stirred and allowed to warm to room temperature for one half hour. The mixture is cooled to 0°C and quenched with ice. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The collected extracts are washed twice with water. The washed ethyl acetate fractions are collected and the volatile components removed and the residue chromatographed on silica gel which yields the above product.

Example 27

The above product is prepared by reacting 1.9g (10 mmol) of p-hexoxyphenol, 2.1g (20 mmol) 5-chloropentyne, 2.1g potassium carbonate (15 mmol) in 50ml of DMF, 100mg of sodium iodide and heating to 40°C for 16 hours. The reaction mixture is poured into water and extracted with hexane. The organic extract is washed once with 10% NaOH, once with water and once with brine and dried over magnesium sulfate. Removal of the solvent yields a gum. The gum is purified by column chromatography on silica to give the above acetylene product.

Example 28

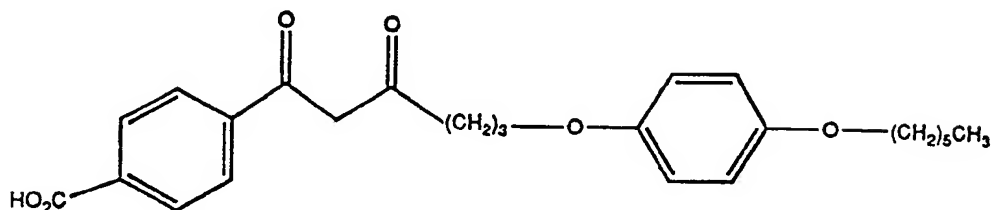
A 1g portion of the acetylene product (3.8 mmol) of Example 27 is dissolved in 25 ml of THF and 10 mg of triphenyl methane is added as an indicator. The solution is cooled to -30°C and 3.4 ml of 1.6M n-butyl lithium (4.1 mmol) is added dropwise until the solution turns red. The solution is back-titrated with the acetylene product until colorless. The solution is cooled to -78°C and 2ml of trimethylsilyl chloride (15.8 mmol) is added. The solution is slowly warmed to room temperature. The reaction is quenched with water and extracted with hexane. The hexane extract is washed once with water and once with brine and dried over MgSO_4 . After removal of the solvent the above product is recovered.

Example 29

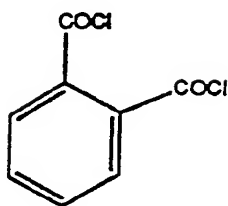
The above compound is prepared by reacting 3 mmoles of the acid chloride product from Example 1 with 1.0g (3 mmoles) of the TMS-acetylene product from Example 28. The acid chloride and the TMS-acetylene product are dissolved in 10cc of dichloromethane and cooled to 0°C. To the reaction mixture is added 0.8g (6 mmoles) of aluminum chloride (AlCl₃) in small portions over ten minutes. The reaction mixture is stirred for about 1.5 hours at 0°C. The reaction is quenched with ice and the mixture is extracted three times with diethyl ether. The extracts are combined and washed once with water and once with brine (saturated NaCl) and dried over magnesium sulfate. Removal of the solvent in vacuo yields the above product.

Example 30

4-[6-[4-(hexyloxy)phenoxy]-1,3-dioxohexyl]benzoic acid



The product of Example 29, 27mg is treated with 2ml of cold H_2SO_4 which has been cooled in an ice bath. The mixture is stirred until all of the product has dissolved. To the reaction mixture is added 1mg HgO . The reaction mixture is maintained cool in an ice bath. Two drops of water are added to the reaction mixture. The ice bath is removed and the reaction mixture is stirred and allowed to warm to room temperature for one half hour. The mixture is cooled to 0°C and quenched with ice. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The collected extracts are washed twice with water. The washed ethyl acetate fractions are collected and the volatile components removed and the residue chromatographed on silica which yields the above product.

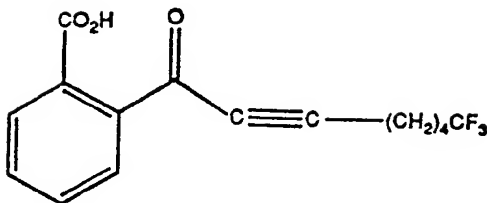
Example 31

The above acid chloride was prepared from phthalic acid by reacting 0.5g (3 mmoles) of phthalic acid with 2cc of $[\text{COCl}]_2$ (23.6 mmoles) in 10cc of benzene and with one drop of dimethylformamide. The reagents were mixed and warmed to 60°C for twenty-four hours. The reaction mixture was cooled to room temperature and the volatile components were removed in vacuo to give the above compound.

Example 32

The above compound is prepared by first preparing a 1-trifluoro-5-bromopentane by the reaction of 5-bromopentanoic acid with SF_4 . The reaction is conducted by mixing 50.166g (0.2771 mmol) of the 5-bromopentanoic acid with 120g (1.111 mmol) of SF_4 and heating in a pressure vessel. A 12.5g (0.3 mmol) amount of NaF was added in 50 ml methylene chloride. The reaction mixture was filtered and washed with about 60 ml of methylene chloride. The methylene chloride was washed once with water and once with NaHCO_3 and once with brine and dried over magnesium sulfate. Removal of the solvent in vacuo gave a brown oil which was distilled and the 25-30°C fraction collected yielding 42.73g of 1-trifluoro-5-bromopentane. Trimethylsilyl-acetylene, 5g (50.9 mmol) was mixed with 50 mg of triphenylmethane in 200 ml of THF and cooled to -50°C and 1.6M n-butyl lithium in hexane was added dropwise (about 33 ml) until a red color persisted. A small portion of trimethylsilyl acetylene was added until the red color disappeared. The mixture was warmed to -20°C and stirred for one half hour. The reaction

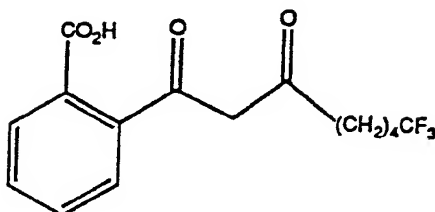
mixture was cooled to -40°C and 10g of the trifluoro-5-bromopentane was added dropwise. Then 50 ml of HMPA was added dropwise and the reaction mixture was stirred and warmed to room temperature. The reaction was quenched with water and was poured into one liter of hexane. The mixture was washed four times with water, once with brine and dried over magnesium sulfate. The solvent was stripped in vacuo to give a brown liquid that was distilled. The fraction boiling between $65-68^{\circ}\text{C}$ was collected and gave 5.0g of the above TMS acetylene product.

Example 33

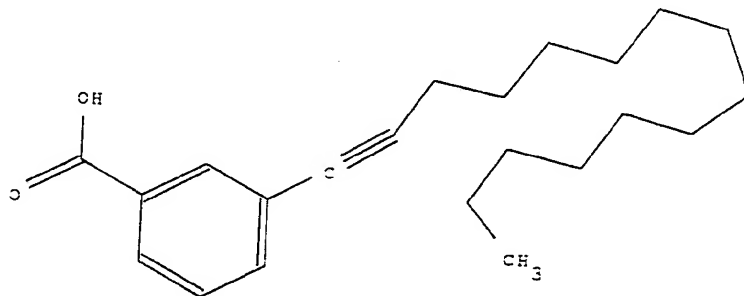
The above compound is prepared by reacting 3 mmoles of the acid chloride product from Example 31 with 0.66g (3 mmoles) of the TMS-acetylene product from Example 32. The acid chloride and the TMS-acetylene product are dissolved in 10cc of dichloromethane and cooled to 0°C. To the reaction mixture is added 0.8g (6 mmoles) of aluminum chloride (AlCl₃) in small portions over ten minutes. The reaction mixture is stirred for about 1.5 hours at 0°C. The reaction is quenched with ice and the mixture is extracted three times with diethyl ether. The extracts are combined and washed once with water and once with brine (saturated NaCl) and dried over magnesium sulfate. Removal of the solvent in vacuo yields the above product.

Example 34

2-(8,8,8-trifluoro-1,3-dioxooctyl)benzoic acid



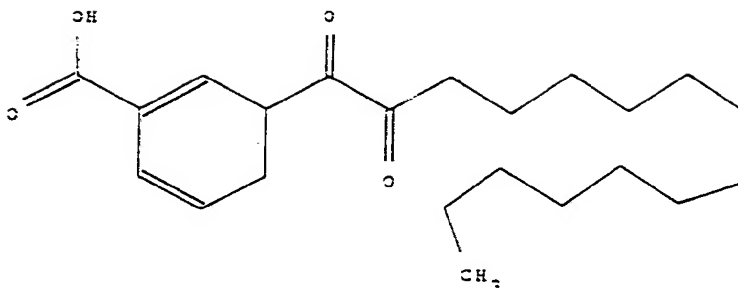
The product of Example 33, 27mg is treated with 2ml of cold H_2SO_4 which has been cooled in an ice bath. The mixture is stirred until all of the product has dissolved. To the reaction mixture is added 1mg HgO . The reaction mixture is maintained cool in an ice bath. Two drops of water are added to the reaction mixture. The ice bath is removed and the reaction mixture is stirred and allowed to warm to room temperature for one half hour. The mixture is cooled to 0°C and quenched with ice. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The collected extracts are washed twice with water. The washed ethyl acetate fractions are collected and the volatile components removed and the residue chromatographed on silica which yields the above product.

Example 35

To a reaction vessel was added m-iodobenzoic acid (1g, 4.03mmoles) 0.83g acetylene (0.4mmoles) of the formula $\text{H}-\text{C}\equiv\text{C}-\text{C}_{13}\text{H}_{27}$, 46mg of a palladium catalyst $\text{Pd}(\text{PPh}_3)_4$ (0.04mmoles) in 10ml of diethylamine. The reaction vessel was degassed with argon. To the reaction vessel was added 0.15g of copper iodide (0.8mmoles). The reaction mixture was stirred under argon for 2 1/2 days. The volatile components were removed in vacuo and the residue was heated with 10% hydrochloric acid. The aqueous solution was extracted with ethyl acetate and the extract was washed with 10% hydrochloric acid, water and brine. The extract was dried over magnesium sulfate. The solvent was removed in vacuo to give a brown gummy solid. This residue was flashed with 10% ethyl acetate-90% hexane-1% acetic acid to yield 1.19g (3.6mmoles) of a white solid of the above identified compound.

Analysis Calculated: C, 80.44; H, 9.82

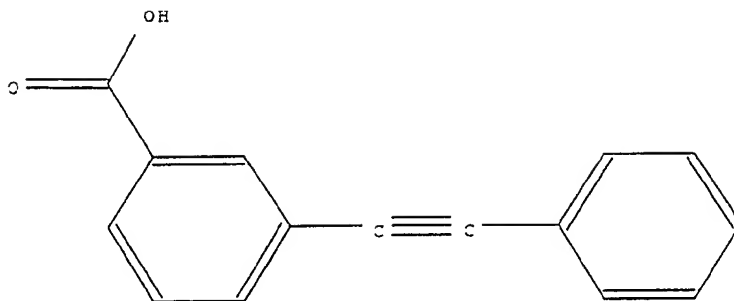
Found: C, 80.65; H, 10.08

Example 36

The compound of Example 35, 0.33g (1mmole) was taken up in a solvent mixture consisting of 4.6ml of CCl₄, 4.6ml of CH₃CN and 7ml of water followed by addition of NaIO₄ (0.88g, 4.1mmoles) which was added in one portion. The reaction mixture was stirred for 10 minutes until a clear solution (two phase) formed. To the solution was added 0.0029g (0.022mmoles) of RuO₂. The reaction mixture was stirred for about 18 hours at room temperature. The reaction mixture was transferred to a separatory funnel and the organic layer separated. The aqueous layer was extracted with dichloromethane. The combined extracts were dried over magnesium sulfate and filtered through celite. Evaporation of the solvent followed by chromatography on silica eluting with 2:1 hexane-diethylether (1% HOAc) yielded 0.12g of the above identified compound.

Calculated: C, 73.30; H, 8.95

Found: C, 73.11; H, 8.94

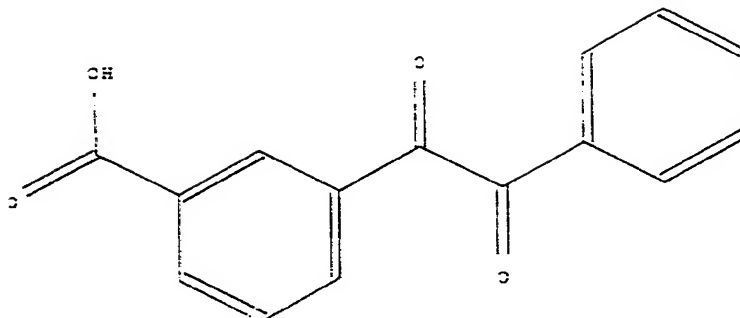
Example 37

In a reaction vessel was added 3g of m-iodobenzoic acid (12.1mmoles) and 1.53g of acetylene (15mmoles) of the formula $\text{Ph}-\text{C}\equiv\text{C}-\text{H}$. To the reaction vessel was added a palladium catalyst 0.085g (0.121mmoles of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in 30ml of diethylamine. The vessel was evacuated and purged with carbon monoxide and the reaction mixture was heated in an oil bath to about 90°C for 2 hours. After such time the reaction was monitored by TLC to determine completeness for the reaction. Upon completion of the reaction, the reaction mixture was cooled to room temperature. The volatile components were removed in vacuo leaving a residue of a dark red solid. The residue was crystallized from diethyl ether and hexane and washed with hexane to give a yellow solid of about 1.64g of the above compound.

Analysis Calculated: C, 81.07; H, 4.54

Found: C, 80.49; H, 4.77

Calculated for $0.1\text{H}_2\text{O}$: C, 80.41; H, 4.59

Example 38

The product of Example 37, 0.22g (1 mmole) was taken up in a solvent consisting of 4.6ml of CCl_4 , 4.6ml of CH_3CN and 7ml of water to which was added NaIO_4 (0.88g, 4.1mmoles). The reaction mixture was stirred for 10 minutes until a clear solution (two phase) developed. To the reaction mixture was added 0.0029g (0.022mmoles) of RuO_2 . The reaction mixture was stirred for approximately 18 hours at room temperature. The mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined extracts were dried over MgSO_4 and filtered through celite. Evaporation of the solvent followed by chromatography on silica eluting with 2:1 hexane/diethyl ether (1% HOAc) yielded 0.156g of the above identified compound.

Analysis Calculated for $0.1\text{H}_2\text{O}$: C, 70.37; H, 4.02

Found: C, 70.23; H, 4.07

ASSAY FOR LTB₄ AND PGE₂ PRODUCTION BY HL-60 CELLS

HL-60 cells were induced to differentiate into granulocytes by a 4 day incubation with 0.8% (v/v) N,N-dimethyl formamide as disclosed in Fontana et al., Proc. Natl. Acad. Sci. 78 (6):3863-3866 (1981); Agins et al., Biochem. Biophys. Res. Comm. 126, 143-149 (1985); and Bonser et al., Biochemistry 20: 5297-5301 (1981). Prior to performing the assay, differentiated HL-60 cells were washed once with Hanks' balanced salt solution containing 0.35 mg/ml sodium bicarbonate and 10 mM HEPES pH 7.35 (HBSS). HL-60 cells (3×10^6 cells/ml) were pre-incubated with the compound tested or a control vehicle at 37°C for 10 minutes, followed by 5 minute incubation with 5×10^{-6} M calcium ionophore A23187 in a final volume of 1.0 ml. After incubation, the cells were pelleted by centrifugation and the LTB₄ and PGE₂ in the supernatant were quantified by radioimmunoassay. IC₅₀ values (means +/- S.E.) for compounds herein that were tested are shown in the following Table and represent the concentrations of the compound required to inhibit 50% of LTB₄ or PGE₂ production by HL-60 cells stimulated with the calcium ionophore A23187.

HUMAN SYNOVIAL FLUID PHOSPHOLIPASE A₂ (HSF-PLA₂) ASSAY

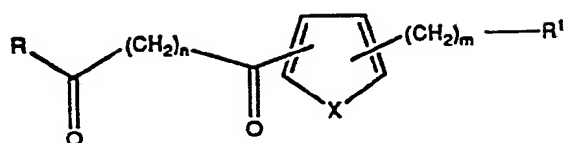
Human synovial fluid phospholipase A₂ was purified approximately 5000 fold following the procedures of Franson et al., Lung 160, 275-284 (1982) and Fawzy et al., Bio Phys. J. 49, 533a (1986). Following purification the enzyme activity was measured by established methodology using [¹⁴C]-oleate-labeled, autoclaved E. coli as the substrate as also shown in the above noted references. The assay was performed in a final volume of 100 µl containing 50 mM HEPES (pH 7.0), 150 mM NaCl, 5mM CaCl₂, 7 nM [¹⁴C]-oleate-labeled E. coli phospholipid and with or without the compound from one of the examples herein undergoing an assay. The compound or control vehicle was pre-incubated with the PLA₂ for 5 minutes followed by addition of the E. coli substrate to initiate the reaction. The reaction was maintained at 37°C for 30 minutes and then terminated by the addition of 2 ml tetrahydrofuran (THF). The reaction product, [¹⁴C]-oleic acid, was extracted using a 1 ml Bond Elut-NH₂ Solid phase extraction column. The IC₅₀ value for the compound (mean +/- S.E.) is given in the following Table and represents the concentration of the compound required to inhibit 50% of the PLA₂ activity.

TABLE

<u>Example #</u>	<u>HSF-PLA2 IC50 μM</u>	<u>LTB4 Biosynthesis</u>	
		<u>inhibition cells IC50 μM</u>	
		<u>Human PMNs</u>	<u>HL60 Cells</u>
5	1.7	1.2	1.5
4	90		
9	2.7	3.5	4.7
19	48	3.0	
15	1.9	2.7	
22	16	2.7	

CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, -CH=CH-, or -CH=N-;

wherein R¹ is -CO₂R² or tetrazole;

wherein R² is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

-(CH₂)_pCF₃ or -(CH₂)_qR³ wherein R³ is alkoxy, phenoxy

or alkoxy substituted phenoxy wherein the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

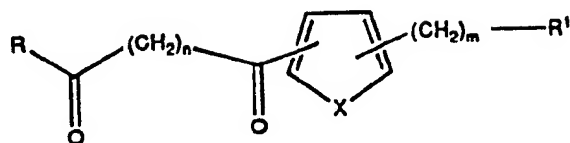
wherein m is 0, 1, 2, or 3.

2. A compound as recited in Claim 1 wherein X comprises -CH=CH-.

3. A compound as recited in Claim 2 wherein m is zero.
4. A compound as recited in Claim 3 wherein R¹ is -CO₂H.
5. A compound as recited in Claim 4 wherein R comprises an alkyl group of 10 to 15 carbons.
6. A compound as recited in Claim 5 which is 3-(1,3-dioxohexadecanyl)benzoic acid.
7. A compound as recited in Claim 5 which is 4-(1,3-dioxohexadecanyl)benzoic acid.
8. A compound as recited in Claim 3 wherein R¹ is tetrazole.
9. A compound as recited in Claim 8 wherein R comprises an alkyl group of 10 to 15 carbons.
10. A compound as recited in Claim 9 which is 1-[3-(1H-tetrazol-5-yl)phenyl]-1,3-hexadecadione.

11. A compound as recited in Claim 1 wherein X is $-C=N-$.
12. A compound as recited in Claim 11 wherein R^1 is $-CO_2H$.
13. A compound as recited in Claim 12 which is 6-(1,3-dioxohexadecanyl)-2-pyridinecarboxylic acid.
14. A compound as recited in Claim 1 wherein X is $-O-$.
15. A compound as recited in Claim 14 wherein R^1 is $-CO_2H$.
16. A compound as recited in Claim 15 which is 5-(1,3-dioxohexadecanyl)-2-furancarboxylic acid.

17. A pharmaceutical composition comprising a compound of the formula



or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, $-\text{CH}=\text{CH}-$, or $-\text{CH}=\text{N}-$;

wherein R^1 is $-\text{CO}_2\text{R}^2$ or tetrazole;

wherein R^2 is hydrogen, alkyl of 1 to 6 carbons or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons, $-(\text{CH}_2)_p\text{CF}_3$ or $-(\text{CH}_2)_q\text{R}^3$ wherein R^3 is alkoxy, phenoxy or alkoxy substituted phenoxy wherein

the alkoxy group has from 1 to 8 carbons;

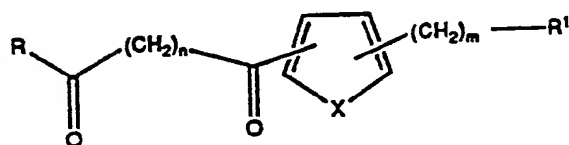
wherein p and q are integers from 0 to 20;

wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3, and a

pharmaceutically acceptable carrier.

18. A method for the treatment of mammals exhibiting an LTB₄ mediated inflammatory condition, comprising administering a compound of the formula



or a pharmaceutically acceptable salt thereof

wherein X is oxygen, sulfur, -CH=CH-, or -CH=N-;

wherein R¹ is -CO₂R² or tetrazole;

wherein R² is hydrogen, alkyl of 1 to 6 carbons

or a pharmaceutically acceptable cation;

wherein R is an alkyl of from 1 to 20 carbons,

-(CH₂)_pCF₃ or -(CH₂)_qR³ wherein R³ is alkoxy,

phenoxy or alkoxy substituted phenoxy wherein

the alkoxy group has from 1 to 8 carbons;

wherein p and q are integers from 0 to 20;

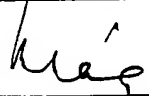
wherein n is 0 or 1; and

wherein m is 0, 1, 2, or 3.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/03572

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07C65/32; C07C65/34; C07C59/90		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0 040 286 (PHOENIX CHEMICAL CORPORATION) 25 November 1981 see claims 1,5,7 ---	1-7
X	US,A,4 381 360 (LEISTNER ET AL.) 26 April 1983 see claims 1,19,22,23,26,38,42,44 ---	1-7
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10 SEPTEMBER 1992	21 SEP 1992	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	KLÁG M. J. 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9203572
SA 61156**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/09/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0040286	25-11-81	JP-C- 1517145	07-09-89
		JP-A- 56099254	10-08-81
		JP-B- 63003905	26-01-88
		AT-T- 11277	15-02-85

US-A-4381360	26-04-83	None	
